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Torque Teno Virus Load and Acute Rejection after Orthotopic Liver Transplantation

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FS: designed the study, analyzed and interpreted the data, wrote the manuscript.

AP: performed overall experiments, analyzed data, edited and approved the manuscript.

SML, CVD, EG, IM, NM, BM, PV, NS, JS, YC: provided substantial contributions to the conception of the work, participated in clinical data collection, edited and approved the manuscript.

LK: provided substantial contributions to the conception of the work and to acquisition of data, interpreted the data, edited and approved the manuscript.

ER: interpreted the data, provided overall research supervision and wrote the manuscript.

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ABBREVIATIONS PAGE

TTV: Torque Teno Virus

OLT: orthotopic liver transplantation

STCS: Swiss Transplant Cohort Study

PCR: Polymerase chain reaction

HC: healthy controls

DNA: Deoxyribonucleic acid

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

DSA: donor-specific antibodies

HR: Hazard ratio

CI: Confidence interval

Replication of Torque teno virus (TTV), a nonpathogenic, highly prevalent Anellovirus increases considerably during immunesuppression[1,2]. Recently, Schiemann and coworkers published the inverse association of TTV load with rejection after kidney transplantation[3]. We here report similar findings in 39 patients [median age 60 (range 1-73) years, male 59%] enrolled in the Swiss Transplant Cohort Study (STCS) after orthotopic liver transplantation (OLT) for liver disease of viral (33%), toxic (10%) or other (57%) origins.

We measured TTV-DNA levels by real time PCR[4] at time of transplantation and, at 6 and 12 months posttransplant for the 19 patients with available serum samples. Seventy-four healthy subjects served as controls (HC). TTV-DNA was detectable (detection limit 25 viral copies/ml of plasma) in 29/39 (74%) patients at transplantation, a prevalence similar to the one observed in controls (51/74, 69%; p=0.8035, χ^2 test). However, median TTV-DNA levels were significantly higher in OLT recipients (median $4.54x10^3$ copies/ml, range 25-$1.2x10^8$) compared with controls (median $1.7x10^2$ copies/ml, range 25-$5.4x10^4$; p=0.0014, Mann–Whitney U test) [Figure 1A]. As shown previously [1,2], TTV-titers in OLT recipients increased significantly after transplantation (median $2x10^6$, range 25-$5.4x10^8$ at 6 months and median $2.2x10^5$, range 25-$1.7x10^7$ at 12 months) [Figure 1A]. We further assessed the relationship between TTV-loads at transplantation with the risk of biopsy proven acute cellular graft rejection (Rejection Activity Index score ≥3 or ≥2 with significant necrosis) during the first year after transplantation. Interestingly, 1-year cumulative incidence of rejection in OLT recipients with detectable TTV-DNA plasma levels at transplantation was significantly lower [21% (95%CI 8%-37%)] than in patients with undetectable TTV-titers [70% (95%CI 28%-90%); p=0.0042, Gray test; Figure 1B].

To account for factors with potential impact on TTV replication and rejection such as age, gender, HBV, HCV and HIV serostatus, underlying disease, number of immunosuppressive drugs used, hepatic encephalopathy and presence of human leukocyte antigen donor-specific antibodies (DSA), we performed a multivariate analysis using Fine-Gray proportional hazard regression for competing events. This analysis confirmed the reduced 1-year cumulative incidence of rejection in patients with detectable TTV titers at time of transplantation [HR $9x10^{-3}$ (95%CI $1x10^{-3}$-$9.2x10^{-2}$; p=0.00008)].

Our results in OLT recipients are in agreement with those reported by Schiemann for kidney transplant recipients and reinforce the results of De Vlaminck and coworkers who found that anellovirus levels in heart and lung transplant recipients with acute rejection episodes were lower than in nonrejecting patients[5]. It is tempting to speculate that a higher immunocompetence in TTV-negative patients at transplantation could be responsible for the higher incidence of rejection episodes observed during the first year after transplantation.

Obviously, our study presents several limitations. First, because serological testing for TTV is currently unavailable, we cannot exclude that some patients are TTV-negative simply because they never have been infected. We do believe however, that the high prevalence of TTV in the population makes this unlikely. Second, the study remains somewhat incomplete because the lack of posttransplant serum samples precluded the analysis of a potential prognostic value of TTV titers after OLT. Larger prospective studies with more patients than in our retrospective pilot study are needed to assess whether monitoring TTV-titers could help identifying patients at higher risk of acute rejection after OLT.

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FIGURE LEGEND

Figure 1. TTV load kinetics and impact on the frequency of rejection episodes after OLT. A) TTV-DNA titers in OLT recipients (filled dots) compared to healthy controls (HC, white dots). Gray filled dots identify patients analyzed at time of transplantation (M0) exclusively. Black filled dots identify patients analyzed at time of transplantation (M0), 6 (M6) and 12 months (M12) after transplantation. Comparison was performed using the Mann–Whitney U test and p values are indicated when significant ($p<0.05$). B) One-year biopsy proven acute rejection cumulative incidence in patients displaying detectable (gray line) and undetectable (black line) TTV-DNA at transplantation. Cumulative incidence of rejection analysis was performed using Gray test with death without rejection as a competing event.

Figure 1